Synthetic control of mammalian-cell motility by engineering chemotaxis to an orthogonal bioinert chemical signal.

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Public Summary:

Scientific Abstract:
Directed migration of diverse cell types plays a critical role in biological processes ranging from development and morphogenesis to immune response, wound healing, and regeneration. However, techniques to direct, manipulate, and study cell migration in vitro and in vivo in a specific and facile manner are currently limited. We conceived of a strategy to achieve direct control over cell migration to arbitrary user-defined locations, independent of native chemotaxis receptors. Here, we show that genetic modification of cells with an engineered G protein-coupled receptor allows us to redirect their migration to a bioinert drug-like small molecule, clozapine-N-oxide (CNO). The engineered receptor and small-molecule ligand form an orthogonal pair: The receptor does not respond to native ligands, and the inert drug does not bind to native cells. CNO-responsive migration can be engineered into a variety of cell types, including neutrophils, T lymphocytes, keratinocytes, and endothelial cells. The engineered cells migrate up a gradient of the drug CNO and transmigrate through endothelial monolayers. Finally, we demonstrate that T lymphocytes modified with the engineered receptor can specifically migrate in vivo to CNO-releasing beads implanted in a live mouse. This technology provides a generalizable genetic tool to systematically perturb and control cell migration both in vitro and in vivo. In the future, this type of migration control could be a valuable module for engineering therapeutic cellular devices.

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